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REVIEW

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Human Nasal Turbinate-Derived Stem Cells for Tissue Engineering and Regenerative Medicine

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Mesenchymal stem cells (MSCs) are multipotent progenitor cells present in adult tissues that are recognized as promising candidates for cell therapy due to their ease of access, straightforward isolation, and capacity for bio-preservation with minimal loss of potency. However, the clinical application of MSCs faces significant challenges, such as donor site morbidity, underscoring the need for alternative sources. Recent studies have suggested that inferior turbinate tissues, which are commonly removed during turbinate surgery, may be a viable donor site for MSCs. Turbinate surgery is a safe and effective procedure frequently performed to alleviate nasal obstruction, a prevalent chronic condition treated by otolaryngologists. This implies that harvesting MSCs from turbinate tissue for tissue engineering and regenerative medicine could serve as a simple, minimally invasive method with faster healing and minimal risk of morbidity or scarring at the donor site. This review highlights previous research indicating that MSCs derived from human turbinate tissues maintain their stability and demonstrate multi-differentiation potential. Therefore, the turbinate could be an alternative to traditional MSC sources for producing functionally competent cells for future clinical applications.

Keywords: Mesenchymal stem cells; Turbinates; Nose; Engineering; Regeneration.

INTRODUCTION

Adult stem cells are undifferentiated cells found in many tissues of the body, capable of self-replication and differentiation into various other tissue types [1]. Initially, stem cells derived from bone marrow were studied and later identified as mesenchymal stem cells (MSCs). MSCs can differentiate into adipocytes, chondrocytes, myoblasts, and osteoblasts [2]. These cells can be isolated not only from umbilical cord blood but also from peripheral blood, and are present in various body tissues, including the placenta, skin, and nerve tissue. However, extracting MSCs from bone marrow is a painful procedure that often requires general or spinal anesthesia [3]. Moreover, the yield of MSCs is relatively low, about 1/105 compared to hematopoietic cells, necessitating their cultivation to achieve clinically significant quantities. This process is costly, time-consuming, and associated with a high risk of infection and cell loss [4]. Additionally, obtaining umbilical cord blood when needed can be challenging, and its long-term storage poses several problems [5]. Recently, to minimize donor morbidity and harvest a substantial quantity of stem cells, researchers have explored using tissues discarded after surgical procedures as a source for MSCs. In plastic surgery, this includes adipose tissue from liposuction; in orthopedics, bone marrow tissue from spinal surgery; and in dentistry, wisdom tooth roots and gum tissue [6]. This review examines the characteristics of MSCs derived from human turbinate tissues, assessing their potential as viable alternatives to traditional MSC sources for producing functionally proficient cells in future clinical applications.

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THE ACCESSIBILITY OF OBTAINING hNTSCs

The human turbinate is a key nasal structure involved in air flow, humidity, and temperature regulation. It is readily accessible during inferior turbinate surgery, a common procedure

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in otolaryngology aimed at alleviating nasal congestion. This tissue can also be easily collected through a quick biopsy of the inferior turbinate under local anesthesia in an otolaryngology outpatient clinic, rather than in an operating room, leaving no external scars post-biopsy. Given the rising prevalence of diseases like allergic rhinitis, which contributes to nasal congestion and is influenced by economic and social environmental changes, the frequency of inferior turbinate surgeries is increasing. Consequently, the harvesting of MSCs and the development of differentiation technologies that utilize the excised and otherwise discarded inferior turbinate tissue are of significant importance [7].

CHARACTERISTICS OF hNTSCs

To determine whether human nasal turbinate-derived stem cells (hNTSCs) exhibit the characteristics of MSCs, we conducted flow cytometry using human MSC surface markers and performed a morphological analysis of the cells. The cells maintained the spindle-shaped morphology typical of MSCs (Fig. 1). The flow cytometry results were negative for the hematopoietic stem cell markers CD34 and CD45, but positive for the MSC markers CD73, CD90, and CD105. Additionally, the cells showed no immunological compatibility issues, as evidenced by a 100% negative result for human leukocyte antigen surface markers, which are critical for histocompatibility [7,8].

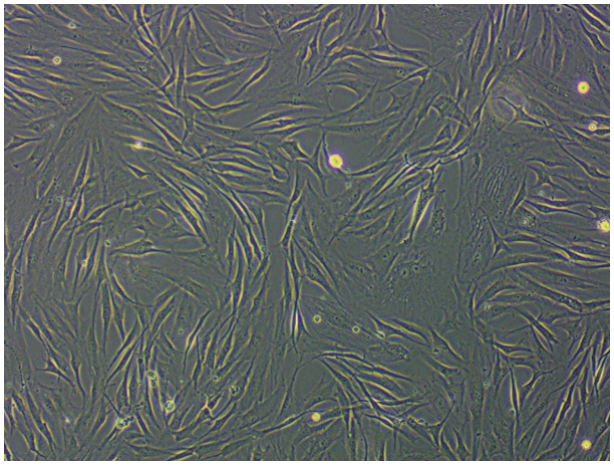


Fig. 1. Illustration of the morphology of human nasal turbinate-derived stem cells (hNTSCs) following primary explant culture. The cells adhered to the culture surface and exhibited a spindle-shaped, fibroblast-like morphology, as observed at 100× magnification.

To confirm whether the characteristics of MSCs are maintained during continuous passage culture, hNTSCs were subcultured through 16 passages. It was observed that the MSC characteristics remained unchanged, in contrast to MSCs derived from other adult tissues, which typically exhibit a reduction in stem cell properties after more than 10 subculture processes [7].

In the process of isolating hNTSCs from turbinate tissue, an analysis of cell numbers and proliferation capacity revealed that approximately 30 times more cells were isolated compared to those from bone marrow and adipose tissue, as reported in previous studies. Additionally, the proliferation capacity in the passage culture process was found to be about 5 times higher (Table 1) [7,9,10].

DIFFERENTIATION POTENTIAL OF hNTSCs

To assess whether the characteristics of MSCs vary with the age of the donors, flow cytometry was conducted using human surface markers. The donors were divided into four age groups for this evaluation. The findings indicated that hNTSCs preserved their characteristics across different donor ages [11].

In a previous study that assessed the differentiation potential of hNTSCs, the microarray method confirmed a distinct expression profile pattern characteristic of cartilage, bone, and neurodifferentiation during the induction of these specific differentiation types. Among the 82 genes that exhibited significant expression differences during neurodifferentiation, glutamine-ammonia ligase (*GLUL*) was identified as having a notable expression difference in olfactory ectomesenchymal stem cells. Additionally, cell adhesion molecule 3 (*CADM3*) is known to be expressed in axons, nerve endings, and synapses. Chimerin 1 (*CHN1*) has been found to be highly expressed in neurons within the hippocampus and cortex, as well as in Purkinje cells in the cerebellum. Thus, the expression of genes associated with neuronal characteristics by inducing neurodifferentiation in hNTSCs has been validated through prior

Table 1. Comparison of the cell yields and proliferation potential of mesenchymal stem cells from different sources

	Human nasal turbinate-derived stem cells	Adipose or bone marrow-derived stem cells
Obtained cell count	6.55×10^3 cells/mg	$0.2–0.29\times10^3$ cells/mg
Cell count ratio in tissue	30	1
Cell number according to subculture	1st subculture: 23.6×10^4 cells	1st subculture: 17.0×10^4 cells
	2nd subculture: 29.0×10^4 cells	2nd subculture: 40.4×10^4 cells
Proliferation rate	Approximately 10 times increase	Approximately 2 times increase

studies [12].

hNTSCs were cultured in osteogenic, adipogenic, and chondrogenic differentiation media for a period of 14 days. After this incubation period, differentiation was evaluated using lineage-specific histological stains and microscopic analysis. Adipogenic differentiation was assessed with Oil Red O stain-

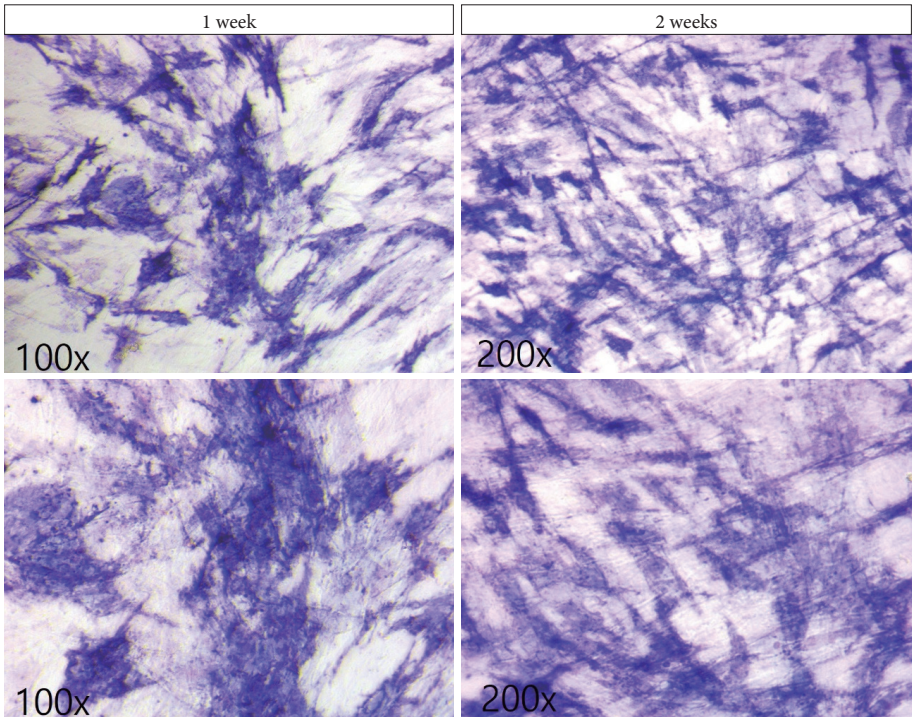


Fig. 2. The osteogenic differentiation potential of human nasal turbinate-derived stem cells, as evidenced by alkaline phosphatase staining after 7 and 14 days of osteogenic induction.

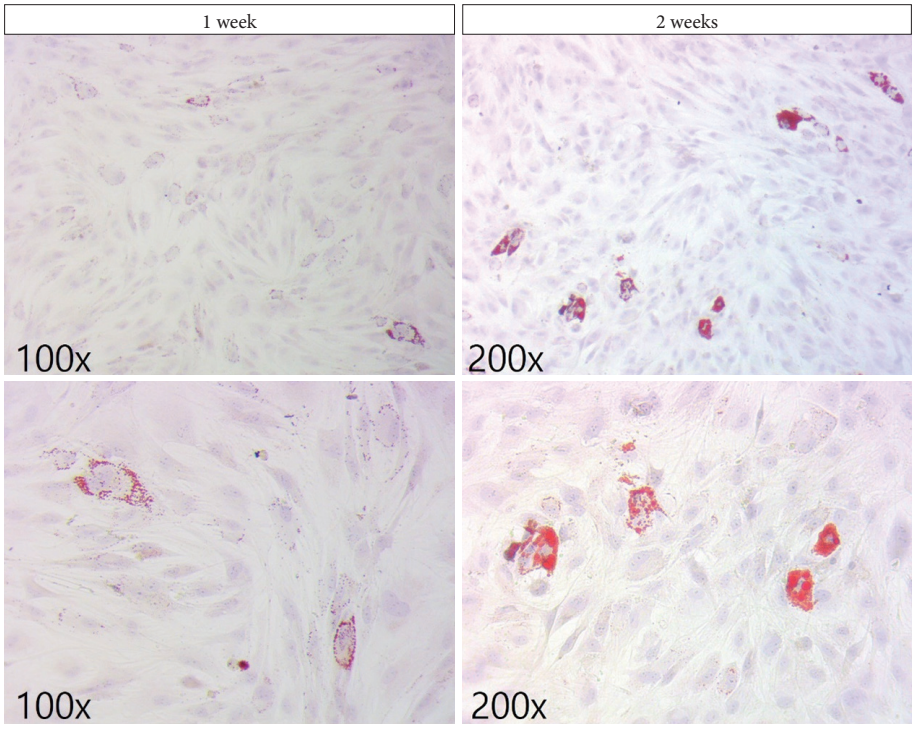


Fig. 3. The adipogenic differentiation potential of human nasal turbinate-derived stem cells, shown by the presence of intracytoplasmic lipid droplets stained with Oil Red O after 1 and 2 weeks of culture.

ing, which visualized lipid droplets indicative of adipocyte formation. Chondrogenic differentiation was examined using Alcian blue stain, which highlighted sulfated components of the extracellular matrix. Osteogenic differentiation was assessed by staining for alkaline phosphatase activity. hNTSCs cultured in osteogenic induction media exhibited notable alkaline phosphatase staining at both 100× and 200× magnification, one and two weeks post-differentiation. Similarly, cells cultured in adipogenic induction media showed significant intracytoplasmic lipid droplet formation, confirmed by Oil

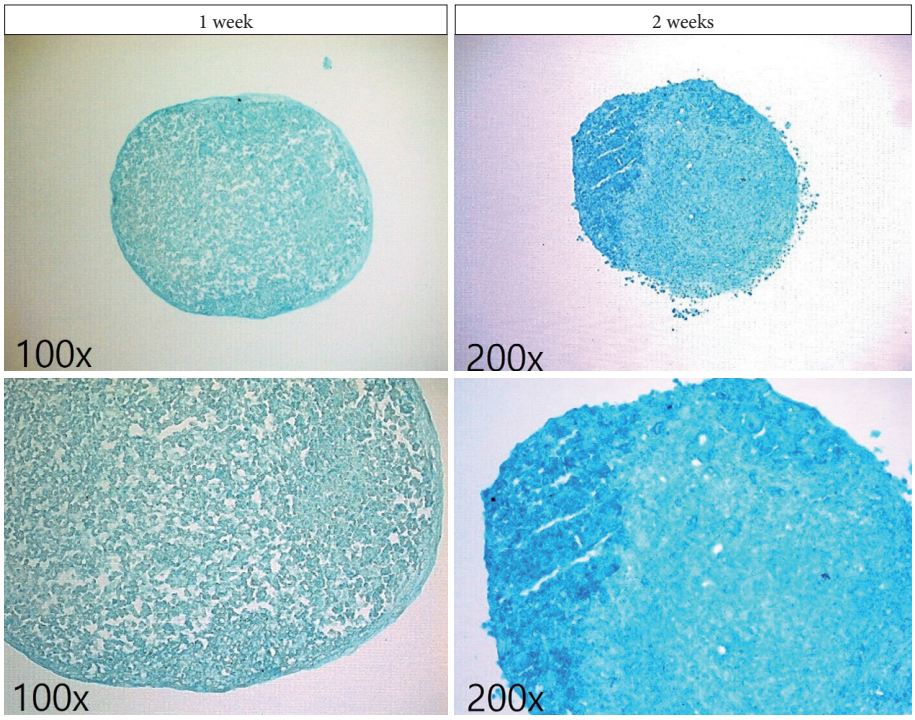


Fig. 4. The chondrogenic differentiation potential of human nasal turbinate-derived stem cells, with histological analysis showing Alcian blue staining after 1 and 2 weeks of differentiation.

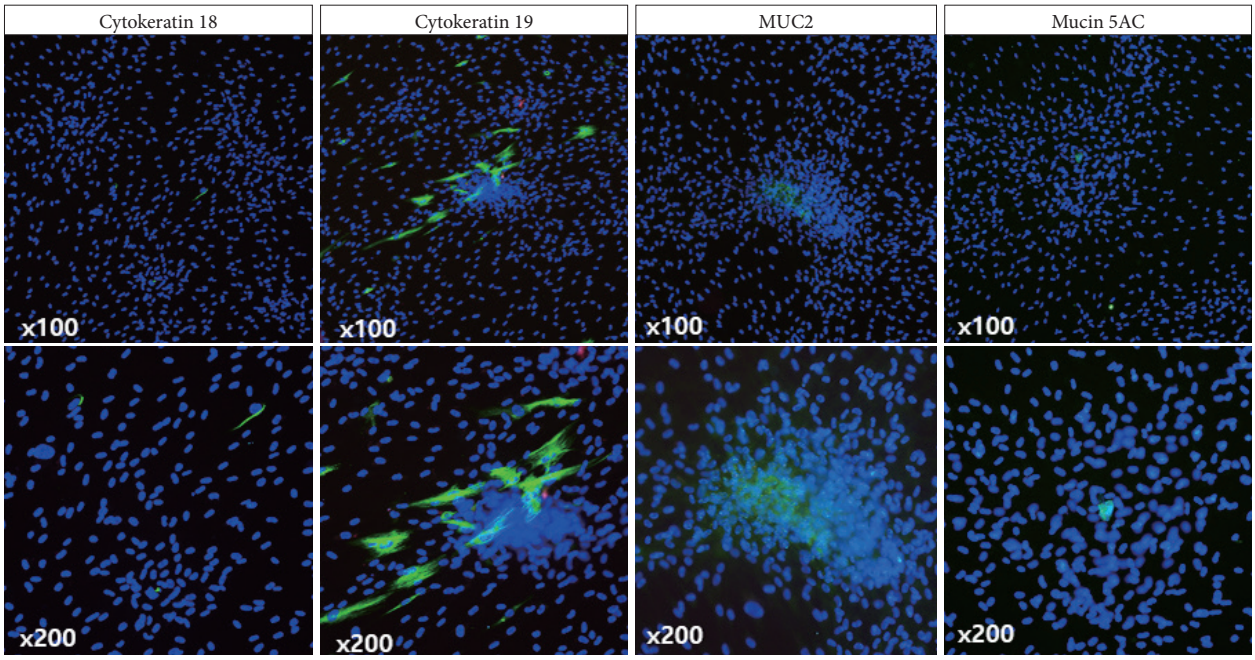


Fig. 5. A histological analysis of the respiratory differentiation of human nasal turbinate-derived stem cells, using immunofluorescence staining for cytokeratin-18, cytokeratin-19, MUC2, and mucin-5AC.

Red O staining. Chondrogenic differentiation was verified by Alcian blue staining, with substantial deposition of the extracellular matrix observed. These findings were visually confirmed through microscopy at 100× and 200× magnifications after one and two weeks of culture (Figs. 2-4) [8,13,14].

In the differentiation experiment involving respiratory mucosal epithelial cells using hNTSCs, the cells were cultured in a membrane form and maintained for 14 days in a specialized medium designed for respiratory epithelial cell culture. The expression of specific markers for cilia, goblet cells, and basal cells, including MUC2, mucin-5AC, keratin-18, and keratin-19, was confirmed through histological analysis (Fig. 5).

CONCLUSION

Research to date has established the presence of hNTSCs, conducted short-term in vitro experiments on their ability to differentiate into multiple tissues such as cartilage and bone, and performed histological and molecular biological analyses. However, for their actual clinical application, it is crucial to verify the stability of hNTSCs and demonstrate their superiority through comparative analysis with MSCs derived from other adult tissues of the same individual. Therefore, it is necessary to assess the multidifferentiation capacity and clinical applicability of these cells through in vivo experiments, such as animal studies. Additionally, further multi-year research is required to compare these cells directly with MSCs derived from other adult tissues, focusing on immunological characteristics, rather than merely confirming that they meet the criteria for MSCs. More research is needed to establish hNTSCs as a more suitable cell source for tissue engineering and to clarify the clinical significance of pluripotency research using these cells. It is anticipated that various researchers globally will conduct such studies in the future.

Ethics Statement

Not applicable

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

Conflicts of Interest

Do Hyun Kim and Se Hwan Hwang are editorial board members of the *Journal of Rhinology* but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Author Contributions

Conceptualization: Se Hwan Hwang. **Data curation:** Se Hwan Hwang. **Formal analysis:** Se Hwan Hwang. **Methodology:** Se Hwan Hwang. **Project administration:** Se Hwan Hwang. **Resources:** Se Hwan Hwang. **Software:** Se Hwan Hwang. **Supervision:** Se Hwan Hwang. **Validation:** Do Hyun Kim. **Visualization:** Do Hyun Kim. **Writing—original draft:** Do Hyun Kim. **Writing—review & editing:** Do Hyun Kim, Se Hwan Hwang.

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